

## CHEMOTHERAPY IN ACUTE UPPER RESPIRATORY INFECTIONS \*

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THE topic assigned to me for this evening's discussion is a difficult one, chiefly because sufficient time has not yet elapsed for a thorough investigation of the possibilities of chemotherapy in upper respiratory infections. I take "chemotherapy" to mean the use of sulfonamides and penicillin. It is true that the sulfonamides have been widely used in the treatment of acute upper respiratory infections, but there is still considerable controversy among practitioners both as to methods and indications for the use of these agents. Penicillin has so recently been released for general civilian use that comparatively little is known about its value in coryza, influenza and their complications. We do know that penicillin possesses certain advantages that render it superior to the sulfonamides. Against susceptible organisms its antibacterial action is many times more potent than that of the sulfonamides. At the same time, even when it is administered in full therapeutic doses penicillin is entirely free of significant toxicity for the host. Unlike the sulfonamides, it is not inhibited by pus or the breakdown products of tissue autolysis. We know of course that most primary upper respiratory infections are of virus origin. It is also a fact that the great majority of viruses, including those causing coryza and influenza, are not subject to control by sulfonamides nor by penicillin.

It has generally been assumed that the complications of coryza and influenza are caused by secondary bacterial invasion, and it is true that cultures from such secondary infections as sinusitis, otitis, mastoiditis and bronchitis regularly yield one or more of the prevalent pathogens of the pneumococcal, streptococcal or staphylococcal groups. However, we need more thorough investigation of the bacteriology of these secondary infections. It has always seemed to me quite likely that the coryza or influenza virus not only attacks the nasopharyngeal mucosa,

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but frequently invades the adjacent tubes and cavities as well, thus preparing the way for secondary infection by a sort of symbiotic process. If this hypothesis is correct, it would explain some of the disappointments incurred with attempts to prevent or cure these complications by chemotherapy alone.

Let us now consider some of these infections in more detail.

#### ACUTE CORYZA

The uncomplicated common cold is a mild infection caused by a filtrable virus which usually runs an afebrile course and clears up completely in four to seven days. Although it is generally recognized that virus infections are unaffected by sulfonamides, many practitioners and otolaryngologists have administered one of the sulfonamides to patients with the common cold with the idea of preventing complications. The practitioners have usually given the drug by mouth; the otolaryngologists have used a spray or powder locally in the nose or throat. Such procedure seemed quite rational and in individual cases the results often appeared to be beneficial. For example, Crowe and his associates<sup>1</sup> at Johns Hopkins Hospital treated a group of nurses with colds by spraying the throat and nasal passages with a 2.5 per cent sulfadiazine in 8 per cent ethanolamine solution (Pickrell's solution). In addition to symptomatic relief they observed a reduction in complications and a decrease in secondary bacterial invaders in the nasopharynx, particularly hemolytic streptococci. The nose and throat were sprayed from eight to twelve times a day for three days, and five to eight times a day for an additional three days. Some sinus involvement was noted in 30 per cent of the control group, whereas in individuals who were sprayed with sulfadiazine, sinusitis developed in only 9.7 per cent. Cough developed in 44 per cent of the controls; in only 8 per cent of the treated group. Some of the patients objected to the taste of the spray. Others complained of irritation of the skin around the external nares. Mild allergic symptoms developed in a small percentage of patients.

Rusk and van Ravenswaay<sup>2</sup> have recently published their results on the oral use of sulfadiazine in the treatment of acute febrile respiratory infections which were seen in a large Army station hospital during the winter of 1942-1943. Doses of drug (3.0 Gm. initially followed by 1.0 Gm. every four hours) similar to those used in pneumonia were admin-

istered until improvement occurred. In the 317 treated patients compared with 314 comparable controls the authors observed no significant difference in either the length of the febrile period or in the period of hospitalization. Contrariwise, Siegel<sup>3</sup> observed decided differences with and without sulfadiazine in alternate groups of feeble-minded children with acute febrile respiratory infections, to which such individuals are particularly susceptible. In this reported series the incidence of serious secondary infections and the duration of the febrile period were considerably lessened.

In the winter and spring of 1942 the writer, in collaboration with Major Norman Plummer and Wilson G. Smillie<sup>4</sup> carried out some experiments on the use of sulfadiazine in the treatment of the common cold at the New York Hospital. The subjects of this study were all members of the personnel of the New York Hospital staff, including nurses, interns, orderlies and technicians. These patients were followed carefully with clinical examinations and nasal and pharyngeal cultures. Of these volunteers with acute respiratory infection, 48 received sulfadiazine by mouth for four days, while 24 received placebo tablets which could not be distinguished from the sulfadiazine tablets. Treatment was

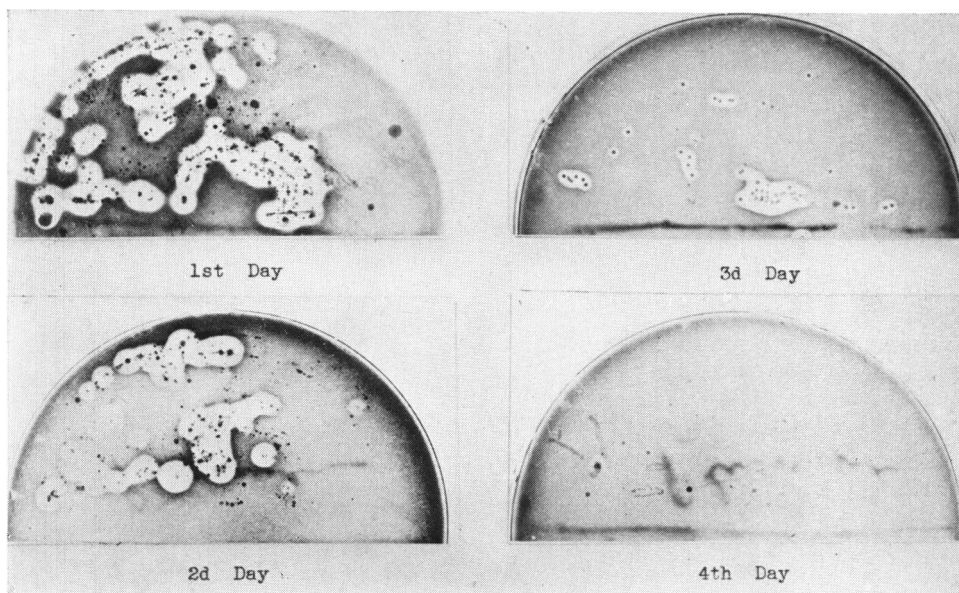


Fig. 1.—Decrease in normal nasopharyngeal flora following oral administration of sulfadiazine. Three grams daily for four days.

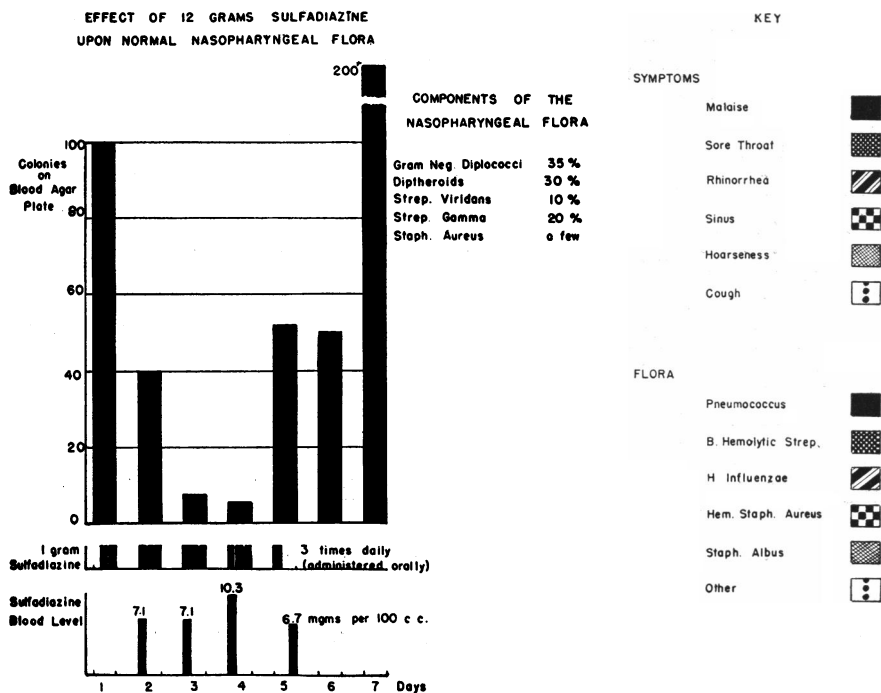


Fig. 2—Effect of 12 Gm. of sulfadiazine on normal nasopharyngeal flora.

Fig. 3.—Key of symbols for symptoms and nasopharyngeal flora.

usually initiated during the second or third day of the cold. Sulfadiazine was taken in oral doses of one Gm. every eight hours for four days, or a total of 12 Gms. Nasopharyngeal cultures were taken at the time treatment was started and at regular intervals, usually every second to third day thereafter, in order to determine the changes that occurred in the nasopharyngeal flora following the treatment. Preliminary cultures on normal subjects indicated that on the dosage of sulfadiazine administered the blood level could reach 4-6 Mgm. per 100 cc. and that at this level there was pronounced reduction in the nasopharyngeal flora. Further cultures indicated a rapid return of the bacterial flora to its former prevalence and distribution within two to three days after sulfadiazine was discontinued.

Fig. 1 illustrates on four blood agar plates marked reduction in the normal nasopharyngeal flora following oral administration of sulfadiazine, 3 Gms. daily for four days.

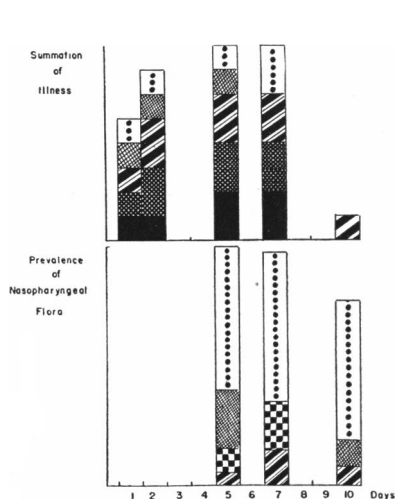


Fig. 4.—(M.H.) Control patient treated with milk sugar tablets. No change in pharyngeal flora; symptoms followed usual course.

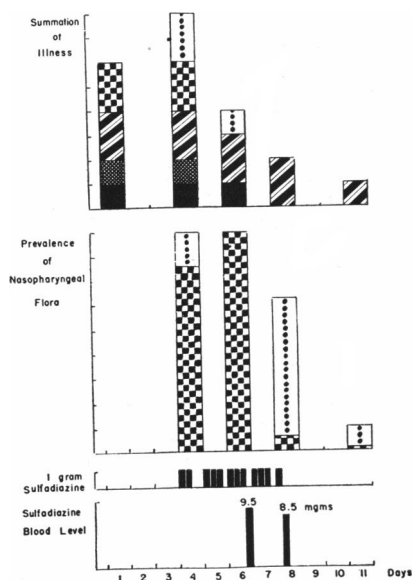


Fig. 5.—(G.F.) This patient shows a favorable clinical and bacteriologic response to sulfadiazine treatment.

Fig. 2 shows the total colony count and correlates it with the blood level of sulfadiazine. This chart also illustrates the rapid return of the organisms to their normal pattern after discontinuance of drug treatment.

Fig. 3 is a key to the symbols used for designating the patient's symptoms and the character of the nasopharyngeal flora.

Fig. 4 represents the course of symptoms and the nasopharyngeal flora in a patient with coryza who received no sulfadiazine, but had milk sugar tablets instead. On the day of onset the usual symptoms of malaise, sore throat, rhinorrhea, hoarseness and cough were present. These symptoms persisted and increased somewhat in severity. The pharyngeal flora remained unchanged during the ten days of observation.

In contrast to this case is the one represented by Figure 5, a patient with coryza who received sulfadiazine treatment. The symptoms cleared up on the 7th or 8th day, and there was a marked numerical drop in the nasopharyngeal flora.

Figure 6 shows a patient with coryza treated with sulfadiazine on the first day of the infection. There was a marked numerical drop in

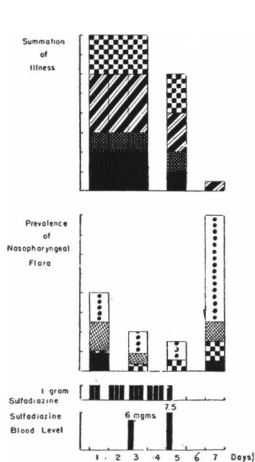


Fig. 6.—(B.P.) This patient shows excellent clinical and bacteriologic response to sulfadiazine but rapid re-appearance of bacteria after discontinuance of the drug.

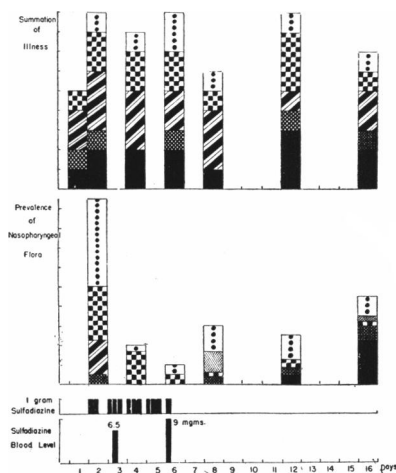


Fig. 7.—Acute coryza and sinusitis. Patient showed good bacteriologic response to sulfadiazine with only slight clinical improvement. With discontinuance of drug, pathogens again became numerous in the nasopharyngeal cultures, and patient developed a severe sinusitis and bronchitis.

the nasopharyngeal flora, but the symptoms persisted for three days and then subsided slowly, disappearing almost completely on the 7th day. When treatment was discontinued, the number of organisms increased, although there was no return of symptoms.

Figure 7 (S.M.) is the graph of a case of acute coryza which started with an irritated throat followed by malaise, rhinorrhea and sinus congestion. Treatment was started on the second day, when the rhinorrhea was severe and there was also an irritative cough. The nasopharyngeal culture on this day showed a heavy growth with a few colonies each of beta hemolytic streptococcus, *H. influenzae* and hemolytic *Staphylococcus aureus*. With the four days of treatment the course was somewhat favorable, the nasopharyngeal culture showing only a few organisms, the hemolytic streptococcus and *H. influenzae* disappearing entirely, and the symptoms being slightly less in evidence. With cessation of sulfadiazine treatment, however, the hemolytic streptococcus returned and type 20 pneumococcus appeared in increasing numbers. At the same time the symptoms became aggravated and the patient developed a severe sinusitis and bronchitis. The suggestion in this case is that if chemotherapy had been continued for a longer period

the secondary infection might have been prevented.

The illustrations cited above afford considerable evidence that sulfonamides do not alter the course of the uncomplicated cold. Furthermore, no outstanding benefits from sulfadiazine therapy were observed in colds complicated by sinusitis and bronchitis. It is quite clear, however, that secondary bacterial invaders can be eliminated or greatly reduced in number by sulfonamide therapy. Such being the case, it is rather surprising that sinus and bronchial complications would sometimes develop in the face of oral administration of sulfadiazine. Perhaps we made a mistake in not continuing the drug for longer than four days. The dosage used would certainly seem adequate, judging by the blood level.

Summarizing our clinical results, it must be admitted that they were not convincing. The average duration of the sulfadiazine-treated colds was 8.1 days, and that of the untreated colds 9.7 days. Of the 48 colds treated, 32 showed no recognizable secondary infection; 16 developed sinusitis, bronchitis or both, either during or after sulfadiazine treatment. Patients who developed complications, however, felt that they were milder in character than they would have been without the drug. The patients who received sulfadiazine were asked for their own opinions on the results obtained, and 34 expressed satisfaction with sulfadiazine treatment; 9 stated they noticed no difference from previous colds. The remainder had no opinion to offer.

#### ACUTE PHARYNGITIS AND TONSILLITIS

As far back as 1937 Long and Bliss<sup>5</sup> reported favorably on the oral use of sulfanilamide in the treatment of pharyngitis and tonsillitis. On the other hand, Rhoads and Afremow<sup>6</sup> in a controlled series of cases of pharyngitis and tonsillitis found that sulfanilamide did not lessen the severity of symptoms, reduce the incidence of complications or shorten the duration of the carrier state. Kernan<sup>7</sup> found that sulfanilamide orally did not alter the ordinary course of tonsillitis, but that complications were fewer when it was used. It seems quite likely that penicillin will replace sulfonamides in the treatment of streptococcal pharyngitis and tonsillitis. For hemolytic streptococcus sore throats I see no particular point in giving either sulfonamides or penicillin unless the infection is severe. In the severe streptococcal throats, either sulfadiazine or penicillin should shorten and mitigate the attack.

Major Norman Plummer writes: "We have had considerable experience with penicillin in the treatment of acute hemolytic streptococcal tonsillitis and pharyngitis. Undoubtedly penicillin is the superior drug against the hemolytic streptococcus and in conditions where there is an accumulation of pus."

#### ACUTE SINUSITIS

Otolaryngologists are pretty well agreed on the value of the sulfonamides in acute sinusitis, especially in the fulminating sinus infections which are often caused by the hemolytic streptococcus. Bowers<sup>8</sup> prefers sulfadiazine or sulfathiazole powder applied directly to the mucous membranes. Silcox and Schenk<sup>9</sup> have used a 5 per cent suspension of microcrystalline sulfathiazole for the treatment of acute and chronic sinusitis, the suspension being instilled directly into the sinuses. In addition to the differences of opinion over the relative value and safety of the different sulfonamides in their crystalline and liquid forms, the value and safety of oral versus local administration also remains controversial. Again, as in the case of tonsillitis and pharyngitis, it seems quite possible that penicillin will displace sulfonamides in the treatment of acute sinusitis.

#### CHRONIC SINUSITIS

In the treatment of chronic sinusitis there is considerable divergence of opinion on the value of sulfonamide drugs. Turnbull<sup>10</sup> reported that a large proportion of patients with chronic sinusitis were benefitted by spraying the nasal cavities with a 5 per cent solution of sodium sulfathiazole. No untoward effects were observed in Turnbull's series of 47 cases. This enthusiasm for the local use of the sulfonamides in chronic sinus infection has not been borne out by later reports, and there have been studies indicating that a 5 per cent sodium sulfathiazole solution is deleterious to the mucous membranes. At this point I would like to cite the case of the following patient who came under my care last summer, and which would seem to indicate that there is a place for penicillin in the treatment of some cases of chronic sinusitis. The local treatments in this patient were carried out by Dr. Stuart Craig.

The patient, Mrs. C., aged 60, had had chronic purulent pansinusitis for many years, accompanied by severe headaches which could be partially relieved by irrigations. The washings invariably yielded a

considerable amount of thick yellow pus which showed a pure growth of hemolytic *Staphylococcus aureus*. For the past year or two the patient had had considerable pain in the joints and muscles which possibly resulted from the chronic sinus infection.

On July 19th the patient was started on intramuscular injections of penicillin, 10,000 units every three hours, except for a midnight injection which was 15,000 units. The 3:00 A.M. injection was omitted. A total of 75,000 units of penicillin was administered each 24 hours, and this was continued for 14 days to a total of 1,000,000 units by the intramuscular route. Simultaneously the patient's sinuses received daily irrigation with penicillin in normal saline, 250 units of penicillin to each cc. of saline. In addition to the daily washing, the nose and throat were sprayed every two hours with a penicillin solution of similar strength. It was found that stronger solutions of 500 units to the cc. caused some irritation to the nasal passages, so they were discontinued.

After 14 days of this treatment the nasal mucosa was much less congested, the amount of secretion gradually diminished, and the character of the discharge had changed from a purulent to a mucoid character. Suction of the nasal passages brought down only a small amount of the material compared with the former large quantity. At the conclusion of two weeks, intramuscular injections were discontinued, but the nasal spray was kept up, the sinuses being washed out two to three times a week.

Three weeks later the headaches had practically disappeared and the mucous membrane presented a healthy pink appearance. A moderate amount of mucus was still discharged, however, from the sinuses.

On September 15th, two months after the institution of penicillin treatment, the mucous membrane still maintained its healthy appearance. The nasal mucosa was much less congested than on last note. There was a small retention still in the upper ethmoid of mucopurulent discharge. No headaches or pain in the sinuses or cranium.

#### OTITIS MEDIA AND MASTOIDITIS

Otolaryngologists are in greater accord on the value of the sulfonamides in acute otitis media. Bowers<sup>8</sup> states that the necessity for mastoidectomy is reduced 50 per cent by the prompt use of the sulfonamides for otitis media, and this view is shared by many other laryngologists and internists as well.

## BRONCHITIS

Acute and subacute bronchitis are common complications of coryza and influenza, and it is the opinion of the writer, based on considerable experience, that the severity and duration of acute bronchitis can often be mitigated by the use of sulfonamide therapy. Naturally this depends a great deal on the bacterial agent responsible for the bronchitis.

So far I have said very little about the use of penicillin for the very good reason that in acute upper respiratory infections my experience with the drug has been very limited. That of course has been the case with most civilian physicians. However, in some of the larger clinics penicillin has already been used experimentally in the treatment of these infections.

Because of the difference of opinion which exists as to the value of sulfonamides in acute upper respiratory infections and because of my limited experience with penicillin, I recently sent out a short questionnaire to twelve of my colleagues who have been particularly interested in the use of sulfonamides and penicillin in acute upper respiratory infections. Six were internists and six were otolaryngologists. All of these men were physicians who have had unusual opportunity to study these drugs in large metropolitan clinics. The responses were interesting and rather surprisingly consistent.

The first question was: "Do you advocate the use of sulfonamides in the treatment of uncomplicated coryza and influenza?" Eight of the 12 physicians gave an unqualified "No" to this question. Four otolaryngologists advocated the use of sulfonamides both locally and orally in severe infections with the aim of preventing complications. For local use, four of the otolaryngologists recommended Pickrell's solution, 2.5 per cent solution of sulfadiazine in 8 per cent triethanolamine solution.

2. Do you favor the use of sulfonamides in the treatment of acute sinusitis?

The response of all twelve to this question was "Yes", and 11 agreed that the drug was beneficial in shortening the course of the infection. One otolaryngologist expressed some doubt.

V. B. Hirst writes: "I have used the sulfonamide drugs locally in the treatment of sinuses with excellent results. The treatment has been with irrigation. In the past two or three years we have shortened the course of these cases very much, even the very foul types, and I am

sure have prevented a lot of surgery."

John Kernan writes: "At times the sulfonamides seem to work magic, especially on acute sinuses. However, much more careful checking should be done with cultures in order to select the proper drug to combat the particular organism involved in the case."

3. Do you favor the use of sulfonamides in *chronic* sinus infections, especially those of *Staphylococcus aureus* origin?

There was very little enthusiasm expressed by either the internists or the otolaryngologists for sulfa therapy in this condition. Practically all agreed that the results were very disappointing, and this was true whether the drug was used orally, as it was by the internists, or locally by the otolaryngologists.

4. Has oral administration of sulfonamides any advantage over the local use of the drug?

Four internists and four otolaryngologists preferred oral administration; four otolaryngologists employed both methods.

Walsh McDermott believes that oral administration has definite advantages. As he expresses it: "Sulfonamide is not an antiseptic solution, so must be taken up by the bacteria deep in the lesion. It seems to me the only way this could occur consistently would be if the blood supply of the infected lesion carried sufficient quantity of the drug. In addition, there is a strong suspicion, but no unequivocal proof, that local use of sulfonamides leads to increase of sensitization to the drug."

5. Do you advise sulfonamides as routine in the treatment of acute otitis media?

All answered "Yes", except one otolaryngologist who voted "No" because in his opinion they masked the onset of mastoiditis. The 11 who voted "Yes" were all convinced that the oral, or both oral and local use of sulfadiazine markedly reduced the incidence of mastoiditis and other ear complications.

Frank Horsfall writes: "Acute otitis media seems to me to be definitely improved, sometimes markedly so, by the use of sulfonamides in full therapeutic doses."

6. Will penicillin treatment shorten a cold?

Three answered "No". Four were in doubt. Five had had no experience with penicillin in the treatment of common colds.

7. Is penicillin of value in the treatment of acute sinusitis and acute otitis media?

Six physicians (four internists and two otolaryngologists) replied "Yes"; one said "No".

Francis Blake writes: "Penicillin will cure many cases of otitis that have failed to respond satisfactorily to sulfonamides. We have treated about 40 cases, the majority being due to *Streptococcus hemolyticus*, many with mastoiditis, some with beginning meningitis. The response has been almost perfect in hemolytic streptococcus infections, and very good in staphylococcus and pneumococcus infections. Penicillin was of no value in *Hemophilus influenzae* infections."

8. What success have you had with penicillin in the treatment of chronic sinusitis?

Two internists and one otolaryngologist replied "Good". Two otolaryngologists answered "Poor". One gave a qualified answer.

9. Have you used penicillin locally or parenterally for these infections?

Five internists had used the drug only by the parenteral route. One both parenterally and locally. The otolaryngologists have usually employed penicillin by both methods, though one had used it only locally. The dilution of penicillin for local use varied considerably, all the way from 100 units to 2000 units per cc. of saline solution. The tendency, however, was toward the weaker dilutions.

Stuart Craig writes: "The local use of sulfonamides, except in selected cases, is not outstandingly effective. The administration of even heavy doses for chronic cases with degenerative changes and thickened membranes has not proved effective in our hands. From the limited opportunity we have had to use penicillin locally in the sinuses, I would believe that it offers great promise when it can be used for the treatment of both acute and chronic sinusitis with no restrictions as to the amount available."

10. Have you seen allergic reactions, such as fever and drug rashes from the local use of sulfonamides?

Four internists answered "No". One had seen a few allergic reactions. It was interesting that 4 out of the 6 otolaryngologists replied "Yes" to this question, suggesting that reactions were more likely to occur from local than from oral use of the drugs.

Wesley Bowers writes: "It seems that we shall always have to bear in mind that using sulfa drugs for trifling conditions may render the patient sensitive to them, so that when they are badly needed for

meningitis or pneumonia, the patient would be forced to go without them."

Walsh McDermott writes: "I have seen allergic reactions in patients receiving sulfonamides by mouth who gave a history of previous use of the drug locally."

12. Have you seen allergic reactions following the use of penicillin?

Three internists replied "Yes", three "No". The otolaryngologists all replied "No".

McDermott says: "Febrile spikes as high as 40° C. have occurred following intramuscular injections of penicillin in previously afebrile patients. I have also seen two patients with definite serum sicknesslike syndrome following penicillin therapy, characterized by urticaria, peri-orbital edema, myositis, arthralgia and fever."

Summarizing the questionnaire, we can make the following fairly consistent generalizations:

1. There is little or no enthusiasm for the use of sulfonamide drugs for the treatment of the common cold and influenza. A few otolaryngologists recommend the drug to prevent complications, but they are in the minority.

2. Both internists and otolaryngologists are enthusiastic over the use of sulfonamide therapy in acute sinusitis. They are much less enthusiastic concerning such treatment in chronic sinusitis.

3. Practically all are agreed that sulfonamides are valuable in the treatment of acute otitis media as a means of preventing mastoiditis.

4. There is no enthusiasm for the use of penicillin for the treatment of the common cold, but there is almost complete uniformity of opinion that penicillin is of value in the treatment of acute sinusitis and acute otitis media.

5. There is only moderate enthusiasm for penicillin therapy in chronic sinusitis.

6. All are agreed that successful therapy with either sulfonamides or penicillin is in large measure dependent upon the type of bacteria responsible for the infection.

7. Allergic manifestations are occasionally seen with both sulfonamides and penicillin, usually in the form of an urticarial rash.

8. Oral administration of sulfonamides and parenteral injection of penicillin are favored over local application of these agents. Combined systemic and local treatment is also popular with both groups.

## COMMENT

One fact seems to stand out clearly as a result of this discussion. There is no indication for the administration of either sulfonamides or penicillin in the treatment of ordinary coryza or grippe. As McDermott says: "With the ordinary cold I see no point in taking the risk of sulfonamides or the *discomfort* of penicillin."

In certain selected cases where the patient knows from past experience that his cold will probably be followed by some complication, one might be justified in using either sulfadiazine or penicillin, but even in these cases there is often some doubt as to the desirability of the procedure.

There is something quite Utopian about the eagerness with which both the medical profession and the laity search for a cold cure, yet when all is said and done, in the vast majority of cases, the common cold is a trivial infection. It makes us uncomfortable for a few days, but usually (with the help of aspirin, atomizers and Scotch whiskey!) we keep at our routine duties. There is a group of patients, of course, for whom the common cold is a much more serious problem. They know from past experience that complications in the sinuses or trachea are going to follow. In a good many children the middle ear has a rather terrifying way of lighting up with every coryza. It is in this group of patients that chemotherapy has its important field. The writer's own experience and that of the physicians whom he has consulted in this questionnaire indicate that sulfonamides and penicillin both have a place in the treatment of these complications. As we obtain more experience penicillin may prove to be the preferable agent. In fact it may entirely replace the sulfonamides.

I don't believe that chemotherapy would be generally successful in any sinus infection that was not at the same time receiving adequate surgical drainage. With drainage, chemotherapy, either sulfadiazine or penicillin, should be effective in properly selected cases. A good deal more investigation will have to be done before dogmatic answers can be arrived at. In the meanwhile it would seem the wiser course for the practitioner to limit his use of these agents to the treatment of sinusitis, otitis, bronchitis and the other less prevalent complications of acute upper respiratory infections.

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